REMARKS/ARGUMENTS

Claims 1-26 have been canceled and claims 27-33 are currently pending. Claims 27 and 31 are amended to include gene names as suggested by the Examiner. Claim 32 is amended to include "an" for antecedent basis. Claim 33 was amended to depend from claim 32.

Objections to Spelling

Examiner suggests that the genes be written in italics in the claims as needed. However, claim 27 and 31 correctly refer to the protein encoded by the gene in capital letters, while the genes are already in small letters and italics. To accommodate Examiner, Applicants have changed the claims to actually name the genes on first recitation. This does not change claim scope, but merely clarifies what is the gene and what protein in encoded thereby.

Objections to Table 2

Table 2 has been amended in rows 9 and 10 (underlined) to include expression of ATF as described in Example 7, page 12. The pKmAT plasmid contains an acetyl transferase as described in Vadali, *et al., "Applicability of CoA/acetyl-CoA manipulation system to enhance isoamyl acetate production in Escherichia coli,"* Met. Eng. 6:294-9, at Table 2 (2004) (showing that pKmAT contains ATF). The pUC19 plasmid is a control vector and pRV380 is a PANK expression vector as described in Table 1.

Claims 27 and 32 Rejected as Indefinite

The Examiner has rejected claim 27 as indefinite for failure to state a "purpose of the increase of the CoA flux by transforming a cell with genes (i), (ii), and (iii)." Applicants respectfully note that claim 27 **expressly states** a purpose of the transformation as "thereby increasing CoA flux relative to said bacterial cell without said recombinant genes." Increasing CoA flux is, of course, useful because the increased flux can be used to drive reactions that require the cofactor. Thus, Applicants do not understand what more is required and request clarification of the rejection—Is the Examiner requiring that further explanation of utility be expressly recited in the claim? Or asserting that Applicants have failed to provide a "specific and substantial utility"? Applicants are unaware of any statutory authority for requiring the

claims to explain utility, nor any evidence proving that Applicants' presumption of utility is overcome. *See* MPEP 2107.02 ("an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement"). Thus, clarification is respectfully requested, and also that the next Office Action **not** be made final in view of the inadequate explanation of this rejection.

Claim 32 recites production of isoamyl acetate, as one example or a reaction that can be driven with the increased flux. Examiner rejects claim 32 as indefinite due to lack of antecedent basis. Thus Applicants have amended the claim to recite "an isoamyl acetate."

Examiner may be suggesting that Applicant limit **all** claims to the purpose of producing isoamyl acetate (Office Action, p. 3, in discussing claim 32). Applicants respectfully decline, however, as that is not the invention, but only one example of the usefulness of increasing CoA flux.

Claim 31 Rejected for Failure of Written Description

Applicants thank the Examiner for reconsideration of the rejection of the claims 27-33.

Claim 31 remains rejected for failure of written description because "bacteria does not produce any alcohol (i.e. all alcohols)" and "addition of an alcohol . . . is necessary." (Office Action, p.4). Examiner further suggests that adding alcohol "may be toxic" and for these reasons Examiner suggests the claim be limited to a specific ("definite") alcohol.[1]

However, Examiners assertions are incorrect and the rejection is not properly supported.

Basic cell biochemistry conclusively establishes that no cell can exist in the absence of alcohol (e.g., glycerol). Even ethanol, which is indeed toxic in high doses, is a fundamental biochemical compound that can enter glycolysis or be converted to an aldehyde, then acetate, and enter fatty acid synthesis, among other things. The fact is that cells contain **many** different alcohols, therefore, an alcohol does **not** necessarily have to be added to the medium.

[1] Examiner continues the same paragraph with reference to claim 27, stating that claim 27 limits "esters to acetate esters". Office Action, p. 4. Claim 27 contains no such language, nor does claim 31. Therefore, this argument seems inapplicable to rejected claim 31.

Additionally, many solventogenic bacteria produce significant amounts of alcohols such as ethanol and butanol. Further, the fact that some alcohols may be toxic in high doses does not render the claim invalid for failure of written description. Even glucose and glycerol are toxic in high doses, but one of ordinary skills knows not to use such high glucose that the bacteria are inhibited or killed.[2] Similarly, anyone of ordinary skill cultivating bacteria knows to keep ethanol within tolerance levels.[3]

Further, the recited class of enzymes known as ATF have a very broad range of specificity and will work on many alcohols.[4] Thus, the claim need not be limited to a particular alcohol as the invention will function for any alcohol endogenous to the cell or added to the medium.

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[2] Ingram *et al., Alcohol tolerance in Escherichia coli,* Pharmacol. Biochem. Behav. 13(S1):191-195 (1980) ("During growth with ethanol, the proportion of 18:1 fatty acid in the lipids of E. coli increases at the expense of saturated fatty acids. The significance of these changes was investigated in terms of growth and survival in the presence of ethanol. Two approaches were used: (1) A comparison of **alcohol tolerance** among strains of E. coli with different fatty acid compositions; (2) A comparison of alcohol tolerance using a lipid mutant in which the fatty acid composition was controlled by exogenous supplements. An increase in unsaturated fatty acid content was beneficial for both growth and survival. We conclude that the alcohol-induced changes in the fatty acid composition of E. coli are part of an adaptive response, compensating for some of the harmful effects of this drug."); Ingram, *Adaptation of membrane lipids to alcohols*, J. Bacteriol. 125(2):670-8 (1976) ("The effects of alcohols of different chain lengths on the fatty acid composition of Escherichia coli K-12 have been examined. My results indicate that these cells radically change their fatty acid composition when grown in the presence of alcohols. These changes represent an adaptive membrane alteration compensating for the direct physicochemical interaction of alcohols with the membrane. Similar adaptive responses of membrane lipids are proposed as a possible biochemical basis for **tolerance to alcohol** and related drugs.").

[3] These facts are believed to be within the common knowledge in the art, but if Examiner disputes same, Applicants will provide a Declaration to that effect. However, the facts are easily ascertained with any basic biochemistry or bacteriology texts.

[4] *See* EC 2.3.1.84 at http://www.chem.qmul.ac.uk/iubmb/enzyme/EC2/3/1/84.html (describing the reaction of the enzyme as "acetyl-CoA + an alcohol = CoA + an acetyl ester."); Verstrepen, *et al. Expression Levels of the Yeast Alcohol Acetyltransferase Genes ATF1, Lg-ATF1, and ATF2 Control the Formation of a Broad Range of Volatile Esters*, Appl. Environ. Microbiol. 69(9):5228–37 (2003) ("The most striking observation in this study is the very broad substrate specificity of the ATF proteins towards the alcohol cosubstrates: all acetate esters that could be monitored with HS-GC and GC-MS seem to be at least partially synthesized by Atf1p and Atf2p. This clearly shows that Atf1p and Atf2p are able to transfer an activated acetate group to a wide variety of substrates with an alcohol group.").

Therefore, Examiners rationale for rejecting claim 31 for failure of written description is factually incorrect and Applicants respectfully request the rejection be withdrawn.

Claims 28, 32, and 33 Rejected for New Matter

Applicants thank the Examiner for reconsideration of the new matter rejection of the claim 31.

Claims 28, 32 and 33 remain rejected for "lack of written description of a bacterium cell having reduced activity of *ack* or *pta*," suggesting that the single mutants are allegedly new matter. Applicants respectfully disagree with this, and suggest the Examiner is improperly limiting the claims based on one exemplification of the invention.

In fact the specification specifically differentiates both enzymes: "the A-CoA **may** be converted to acetyl phosphate by phosphotransacetylase (PTA), **which in turn may** be converted to acetate using acetate kinase (ACK)."[5] Therefore, the specification states that **either** enzyme may act on A-CoA, and each is in fact described as separate.

The specification further describes on multiple occasions the "acetate formation pathway of acetate kinase and phosphotransacetylase"[6] and states that "one or more" pathways can be reduced.[7] The specification continues by providing a specific example reciting the two enzymes separately.[8] Thus, the specification specifically states that one or more pathways can be **reduced** and describes the pathway as composed of **separate** enzymes that can be reduced. This is an explicit description of what is recited in the claim!

The Examiner focuses on the fact that Applicants "received as a **gift** the strain that has mutated both genes *ackA* and *pta*, and this very mutant was used in the claimed method."[9]

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[5] ¶ 28 (emphasis added).

[6] ¶ 40.

[7] ¶ 40 ("the invention shows an enhancement of A-CoA levels through the **reduction** of A-CoA flux through **one or more** A-CoA utilizing pathways.") (emphasis added).

[8] ¶ 40 ("Examples of such A-CoA utilizing pathways include, but are not limited to, acetate formation pathway of acetate kinase and phosphotransacetylase…").

[9] Office Action, p.6.

Therefore, Examiner is apparently suggesting that because Applicants only used a "gift" of a double mutant that the single mutants are not otherwise available. This is not true, as each individual mutant is already available.[10] Thus, the single mutants are publicly available to one of ordinary skill in the art, including inventor Bennett. The prior art conclusively demonstrates that the single mutants were readily available and could be used to reduce activity of the acetate formation pathway. The "gift" nature of the double mutant is irrelevant.

Therefore, because the specification i) describes the enzymes separately and says that either may be used, and ii) states that one or more pathways can be reduced and specifically **names** the **individual enzymes** as an example thereof, and the art shows that iii) single mutants are already available (and in use by inventors), Applicants conclude that the single *ackA* or *pta* mutants are not new matter.

Claim 31 Rejected for Failure of Enablement

Applicants thank the Examiner for reconsideration of the rejection of claims 27-33.

Claim 31 remains rejected because the claim is allegedly not enabled for the use of "any alcohol (i.e. all alcohols)" for the reasons articulated under written description, namely that the alcohol is not specified, that the media must be supplemented, and that alcohols may be toxic.

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[10] *See e.g.*, Boynton, **Bennett**, Rudolph, *Cloning, sequencing, and expression of genes encoding phosphotransacetylase and acetate kinase from Clostridium acetobutylicum ATCC 824,* Appl. Environ. Microbiol. 62:2758-66 (1996) ("The genes pta and ack, encoding PTA and AK, respectively, were cloned and sequenced. . . . This work provided material for gene inactivation . . ."); Green, et al. [and **Bennett**], *Genetic manipulation of acid formation pathways by gene inactivation in Clostridium acetobutylicum ATCC 824*" Microbiol. 142:2079-86 (1996) (describing "[i]nactivation of the pta gene"); Causey, et al., *Engineering Escherichia coli for efficient conversion of glucose to pyruvate*; PNAS 101(8): 2235–2240 (2004) (describing "ΔackA"); Shi, et al., *A Defect in the Acetyl Coenzyme A ↔ Acetate Pathway Poisons Recombinational Repair-Deficient Mutants of Escherichia coli*, J. Bacteriol. 187(4): 1266–1275 (2005) (describing the use of "precise deletions of either ackA or pta"); ESCHERICHIA COLI AND SALMONELLA TYPHIMURIUM: CELLULAR AND MOLECULAR BIOLOGY, Vol. 1. p. 297 (Neidhard ed., Am Society for Microbiology 1987) ("Mutants defective in **either the ack or pta gene are severely impaired in utilizing acetate** as sole carbon source.") (emphasis added) (citation omitted).

Applicants refer Examiner to the above facts under the written description section establishing that every single cell contains many different alcohols, that the medium therefore need not be supplemented unless desired, that many bacteria produce significant amounts of solvent alcohols, and that even if the medium is supplemented with a particular alcohol, it is well within the scope of the ordinary artisan to select alcohol levels that are within tolerance levels.

As an example, Applicants refer to glycerol, a simple alcohol found in **all** cells that can be toxic when used in high levels in the medium. Yet, dozens of recipes include non-toxic levels of glycerol (see. E.g., LB broth + 7.5% glycerol). As another example Applicants refer to the solvent producing bacteria that produce significant amounts of solvents such as ethanol, butanol and the like, each of which need not be added to the medium, yet can be toxic in these bacteria in high levels.

Applicants further note that ATF has very broad specificity. Verstrepen notes "the very broad substrate specificity of the ATF proteins."[11] This is even confirmed by the IUBMB Enzyme Nomenclature which describes the reaction of alcohol O-acetyltransferase (EC 2.3.1.84) as follows:

acetyl-CoA + an **alcohol** = CoA + an acetyl ester[12]

Thus, the enzyme is known and recognized to esterify "an alcohol", not a specific alcohol as suggested by Examiner.

The Examiner has provided no evidence to the contrary. Applicants request the Examiner provide at least one example of an ATF that has a sole substrate and will not react with more than one alcohol, or one example of a bacteria that fails to produce alcohols, or one example of a person of ordinary skill in the art that cannot supplement the medium with an alcohol within the tolerance levels of that bacteria.

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[11] Verstrepen, et al. *Expression Levels of the Yeast Alcohol Acetyltransferase Genes ATF1, Lg-ATF1, and ATF2 Control the Formation of a Broad Range of Volatile Esters,* Appl. Environ. Microbiol. 69(9):5228–37 (2003).

[12] *See e.g.*, http://www.chem.qmul.ac.uk/iubmb/enzyme/EC2/3/1/84.html

Claims 27-33 Rejected as Obvious

The Examiner has rejected claims 27-33 as obvious in light of San, Song, Vallari, Voet, and Yang. The *prima facie* obviousness burden lies on the Examiner to show at least the following: 1) that the art teaches every element of the claimed invention[13], 2) that there is a motivation to combine or modify the art,[14] and 3) that there is a reasonable expectation of success in making that combination or modification.[15] If the *prima facie* case is made, it can be rebutted by showing long felt need, commercial success, unexpected results,[16] or teaching away. *See e.g., KSR Int'l Co*, 127 S. Ct. at 1734, 1740.

Prima Facie Case

Recombinant *pdh* Element Not Taught: The Examiner has not provided a reference teaching "recombinant *pdh* gene." Therefore, the *prima facie* case is not made. Even in the wake of *KSR,* Applicants know of no legal principle that suggests that a *prima facie* case can be maintained where a claimed element is not found in the prior art. Thus, in the absence of this element, the obviousness rejection cannot be maintained because the *prima facie* case is not made.

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[13] *See e.g.*, MPEP 2143.03 ("All Claim Limitations Must Be Taught or Suggested").

[14] KSR did not negate the motivation to combine test, but only cautioned against its rigid application. *KSR Int'l Co. v. Teleflex Inc.*,127 S. Ct. 1727, 1741 (2007) ("When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight . . . a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art . . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.").

[15] *See also,* MPEP 2143.02 entitled "Reasonable Expectation of Success Is Required".

[16] *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 371 (Fed. Cir.2006) ("While a reasonable expectation of success must be shown, in order to show *prima facie* obviousness it is not necessary to show that success was absolutely predictable."); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (discussing the obviousness case and stating that one element is "whether the prior art would also have revealed that . . . those of ordinary skill would have a reasonable expectation of success."). *See also*, MPEP 716.02(a) ("Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness.").

Supplementation with Pantothenate Element Not Taught: Examiner cites Song as teaching supplementation with 60 mM pantothenate when panK is overexpressed. The Examiner reading of Song is insufficiently detailed to understand what it is actually teaching. Song was **required** to supplement with pantothenate because Song used a ΔpanD mutant **abolishing** endogenous pantothenate production.[17] The purpose of using a mutant that cannot produce any pantothenate was to force the bacteria to use the added labeled pantothenate so that its use could be easily tracked by radiolabel. Further, Song actually shows that in spite of the pantothenate supplementation (and *panK* overexpression), CoA was **not** increased![18]

Thus, Song cannot be cited for teaching to supplement pantothenate in the instant case, where the literature in fact teaches that pantothenate is produced in great excess and therefore should **not** need supplementation.[19] Thus, even if the bacteria produces more PANK due the recombinant gene, it should simply be able to retain the normally excreted excess.

Examiner cites Vadali as support to conclude that "a skilled artisan would [conclude] "With the overexpression of [panK], the availability of [pantothenic] acid might be rate limiting

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[17] *See*, Song & Jackowski, *Cloning, Sequencing, and Expression of the PantothenateKinase (coaA) Gene of Escherichia coli,* J. Bacteriol. 174(20): 6411-6417 (1992) (Table 1 of Song showing SJ16 strain used includes a *panD2* mutant; *also*, Material and Methods describing supplementation of SJ16 (*PanD*) strains with labeled pantothenate). *See also*, Rock, Park & Jackowski, *Role of Feedback Regulation of Pantothenate Kinase in Control of Coenzyme A Levels in Escherichia coli,* J. Bacteriol. 185(11): 3410–3415 (2003) ("the **panD** mutation prevented the synthesis of endogenous pantothenate").

[18] Song & Jackowski, *Cloning, Sequencing, and Expression of the PantothenateKinase (coaA) Gene of Escherichia coli,* J. Bacteriol. 174(20): 6411-6417 (1992) ("Cells were grown on extracellular pantothenate concentrations of 10 to 60 uM, and the metabolite levels, including those of **CoA**, acyl carrier protein, and phosphopantetheine, **did not change significantly**").

[19] Rock, Park & Jackowski, *Role of Feedback Regulation of Pantothenate Kinase (CoA) in Control of Coenzyme A Levels in Escherichia coli,* J. Bacteriol. 185(11): 3410–3415 (2003) ("E. coli produces about **15 times more pantothenate than it uses** for CoA biosynthesis, and the excess vitamin is excreted."); Jackowski and Alix, *Cloning, sequence, and expression of the pantothenate permease (panF) gene of Escherichia coli.* J. Bacteriol. 172(7): 3842–3848 (1990) ("Increased copy number of the panF+ allele resulted in increased rates of pantothenate uptake and a significant increase in the steady-state intracellular pantothenate concentration. **Despite the higher levels of pantothenate, the utilization of pantothenate for coenzyme A formation was not elevated**, indicating that pantothenate kinase activity is the dominant regulator of coenzyme A biosynthesis.").

if panK is overexpressed."[20] Vadali is **not** prior art and may not be used in this way. Vadali is the Applicants own work.

Examiner further argues that one might expect to have to add pantothenate since a multicopy plasmid is used, and that supplementation might not be required with just one or a few copies. This is speculation and would require knowledge of the *in vivo* activity and intracellular concentration of the substrate and product and how these each affect the enzyme. Yet this information was not available at the time of filing. The Examiner is requested to provide at least one prior art example of a case where PANK requires supplementation (and not because the pathway is otherwise abolished as in Song).

Thus the cited art does **not** show recombinant *panK* cells require supplementation with pantothenate, and the *prima facie* case is not made.

Motivation to Combine Not Shown: The Examiner makes no showing of a motivation to combine these references. The Examiner doesn't even use the words "motivate" or "motivation." This is facially insufficient to establish a *prima facie* case.

Reasonable Expectation of Success Not Shown: The Examiners' rationale showing a reasonable probability of success is reproduced in its entirety:

> Probability of success in transformation with the genes as very high as evidenced by Song and Jackowski for panK, and by San et al for ATF; as well as, because at the time of invention transformation of bacterial cell with endogenous or exogenous genes was a routine practice. All claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed with no change in their respective functions, and the combination would yielded predictable results to one of ordinary skill in the art at the time of the invention. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole prima facie obvious.[21]

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[20] Office Action, p. 14.

[21] Office Action, p. 11-12.

Clearly this is insufficient to establish that increased flux can be obtained with the three recited genes. First, only **two** of the recited genes are taught by the cited art, and second all the Examiner has established is that there is probable success for the two known **transformations**. Further, conclusory assertions without an articulated rationale or factual basis of support is insufficient as a matter of law. *KSR Int'l Co,* 127 S. Ct. at 1741 ("To facilitate review, this [obviousness] analysis should be made explicit. '[R]ejections on obviousness grounds cannot be sustained by **mere conclusory statements**; instead, there must be some **articulated reasoning with some rational underpinning** to support the legal conclusion of obviousness'") (citation omitted) (emphasis added).

Without a rationale and/or evidence to support a reasonable expectation of success, the *prima facie* case is not made.

Prima Facie case Not Made: Because i) two elements are missing, ii) there is no discussion of the motivation to combine, and iii) there is not a rationale establishing a reasonable expectation of success, the *prima facie* case is not made.

Competent Evidence Required: Personal knowledge or mere argument is **not** competent evidence. *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) (holding that "the Board did not err in determining that Fiers presented no convincing evidence" where applicant only showed "argument ... 'unsupported by competent evidence, entitled to little or no weight and ... unpersuasive in any event.'"); *In re Juillard*, 476 F.2d 1380 (C.C.P.A.) ("arguments cannot take the place of evidence"). The Examiner has provided no competent evidence to indicate that a the three recited genes in combination will lead to increased flux, merely unsupported speculation.

To the extent that the Examiner is relying on personal or common knowledge to supply the missing elements of the *prima facie* case, Applicants expressly challenges such assertions as not properly Officially Noticed. Therefore, Applicants request that Examiner support all findings with adequate evidence pursuant to MPEP 2144.03.[22]

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[22] "When making an obviousness rejection, Office personnel must therefore ensure that the written record includes findings of fact concerning the state of the art and the teachings of the references applied. In certain circumstances, it may also be important to include explicit findings as to how a person of ordinary skill would have understood prior art teachings, or what a person

Hindsight Impermissible: The Examiner continues by citing the **inventors own Declaration** to support the obviousness case (Office Action, p. 12). This is clearly hindsight which is impermissible. *KSR Int'l Co.* at 1742 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

Secondary Indications of Non-Obviousness

Unexpected Flux Increase: A significant increase in isoamyl acetate production illustrates that the strategies of cofactor manipulation and carbon flux enhancement are **synergistic** and much more effective in increasing isoamyl acetate production.[23] Using the combination described herein, led to a **5-fold** increase in Co-A flux.[24] This dramatic increase compared to the control strain is a much larger increase in Co-A flux than could be predicted.

Unexpected Supplementation Requirement: The art teaches that pantothenic acid is in 15 fold excess, therefore should not need supplementation.[25] At the time of filing, it was unexpected to one of ordinary skill in the art that bacteria would require supplementation with pantothenic acid and, without supplementation, increased CoA flux would not be achieved.

CONCLUSIONS

Each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. At the very least, claim 27-30 and 32-33 appear to be free of the art and 112 rejections. Therefore, Applicants request allowance of at least these claims. Applicants

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of ordinary skill would have known or could have done." Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., Fed. Reg., 72(195) (October 10, 2007).

[23] ¶ 63 ("cofactor manipulation and carbon flux enhancement are synergistic").

[24] ¶ 63 ("increase in isoamyl acetate production is about 5-fold, upon simultaneous manipulation of CoA/A-CoA levels and enhancing carbon flux from pyruvate node").

[25] Rock, Park & Jackowski, *Role of Feedback Regulation of Pantothenate Kinase (CoA) in Control of Coenzyme A Levels in Escherichia coli*, J. Bacteriol. 185(11): 3410–3415 (2003) ("E. coli produces about 15 times more pantothenate than it uses for CoA biosynthesis, and the excess vitamin is excreted.").

respectfully request the Examiner contact them if there are any questions or issues that need to be addressed.

The fee for a one month extension is enclosed. It is believed that no additional fees are required for this submission. Should Applicants be incorrect, please charge additional fees and credit any overpayment to Deposit Account No. 50-3420 (reference 31175413-005002 MDB)

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Respectfully submitted,

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